Disease-Targeted treatment improves cognitive function in patients with precapillary pulmonary hypertension

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Abstract: BACKGROUND Patients with pulmonary hypertension (PH) may suffer from cognitive deficits that potentially relate to reduced oxygen delivery and cerebral tissue oxygenation (CTO). OBJECTIVE To evaluate the hypothesis that cognitive function improves with therapy, along with improved CTO. METHODS Twenty incident patients with arterial or chronic thromboembolic PH had CTO monitoring by near-infrared spectroscopy during diagnostic right heart catheterization. Cognitive tests [Trail Making Tests (TMTs), Victoria Stroop tests and the Five-Point Test (5PT)], the 6-min walk distance (6MWD) test, New York Heart Association (NYHA) class and health-related quality of life (HRQoL) were assessed and repeated after 3 months of disease-targeted medication. RESULTS At baseline, 45% of PH patients had cognitive deficits. At 3 months, the patients had improved on the TMT A and the Stroop 2 test [37 s (27; 55) versus 30 s (24; 42), $p < 0.05$, and 18 s (16; 22) versus 16 s (15; 20), $p < 0.01$], whereas CTO remained unchanged. Arterial oxygen saturation, NYHA class, 6MWD and HRQoL had also improved. Baseline CTO was the strongest predictor of cognitive function, even in multivariate analysis including age, 6MWD and HRQoL. Improvements in cognitive function were not associated with changes in CTO. CONCLUSIONS In patients with PH, 3 months of disease-targeted medication resulted in better cognitive function. Although CTO was the strongest predictor of cognitive function at baseline, it did not change during target therapy. The results of this pilot study should be confirmed in an adequately powered controlled trial.

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Disease-Targeted Treatment Improves Cognitive Function in Patients with Precapillary Pulmonary Hypertension

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Key Words

Pulmonary hypertension · Pulmonary arterial hypertension · Chronic thromboembolic pulmonary hypertension · Cognitive function · Cerebral tissue oxygenation · Near-infrared spectroscopy

Abstract

Background: Patients with pulmonary hypertension (PH) may suffer from cognitive deficits that potentially relate to reduced oxygen delivery and cerebral tissue oxygenation (CTO). ***Objective:*** To evaluate the hypothesis that cognitive function improves with therapy, along with improved CTO. ***Methods:*** Twenty incident patients with arterial or chronic thromboembolic PH had CTO monitoring by near-infrared spectroscopy during diagnostic right heart catheterization. Cognitive tests [Trail Making Tests (TMTs), Victoria Stroop tests and the Five-Point Test (5PT)], the 6-min walk distance (6MWD) test, New York Heart Association (NYHA) class and health-related quality of life (HRQoL) were assessed and repeated after 3 months of disease-targeted medication. ***Results:*** At baseline, 45% of PH patients had cognitive deficits. At 3 months, the patients had improved on the TMT A and the Stroop 2 test [37 s (27; 55) versus 30 s (24; 42), $p < 0.05$, and 18 s (16; 22) versus 16 s (15; 20), $p < 0.01$], whereas CTO remained unchanged. Arterial oxygen saturation, NYHA class, 6MWD and HRQoL had also improved. Baseline CTO was the strongest predictor of cognitive function, even in multivariate analysis including age, 6MWD and HRQoL. Improvements in cognitive function were not associated with changes in CTO. ***Conclusions:*** In patients with PH, 3 months of disease-targeted medication resulted in better cognitive function. Although CTO was the strongest predictor of cognitive function at baseline, it did not change during target therapy. The results of this pilot study should be confirmed in an adequately powered controlled trial.

Introduction

Precapillary pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure of ≥25 mm Hg, along with a pulmonary artery wedge pressure of ≤15 mm Hg [1].

PH leads to fatigue and reduced exercise capacity and may be associated with cognitive deficits [2]. Only one study has so far investigated cognitive function in pa-

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tients with pulmonary arterial hypertension (PAH) [2]. Cognitive deficits were found in more than half of PAH patients and mainly presented as worsening in verbal learning, delayed verbal memory, reduced executive function and failed fine motor scores. A decline in cognitive function might also be associated with reduced health-related quality of life (HRQoL), which itself is known to be associated with disease progression [3–6].

PH leads to hypoxemia, mainly due to a reduced cardiac output and mixed venous oxygen saturation ($SmvO_2$), especially during exercise [7], but little is known about cerebral tissue oxygenation (CTO). In healthy and diseased adults, lower CTO has been shown to be correlated with impaired cognitive function [8–11]. The brain is a key factor for exercise limitation in healthy people, and this might especially be true for patients with cardiorespiratory diseases, where a central limiting mechanism protects organs from severe exercise-induced hypoxia [12–15]. In line with this, we have recently shown that PH patients have reduced CTO during exercise and that CTO can be improved by acute pulmonary vasodilation with nitric oxide or supplemental oxygen [13]. However, it is not known whether these favorable effects are maintained after long-term pulmonary vasodilation with PH-targeted therapies.

Therefore, our aim was to study cognitive function in newly diagnosed patients with PAH or inoperable chronic thromboembolic PH at baseline and after 3 months of disease-targeted medical treatment. A further aim was to assess whether cognitive function might be linked to CTO and to study its relationship with functional and exercise capacity, arterial oxygenation and HRQoL [1, 16].

Methods

Patients

This is a single-center study performed at the University Hospital of Zurich between June 2011 and October 2014. Patients with PAH or chronic thromboembolic PH who were scheduled for diagnostic right heart catheterization (RHC) and had planned follow-up (FU) visits were included upon written informed consent. Part of the patients had participated in a previous study that determined the effects of acute vasodilator therapy, supplemental oxygen and exercise on CTO and blood flow during RHC [13]. The study was approved by the Zurich Cantonal Ethics Review Board and registered (Clinicaltrials.gov, NCT01463514).

Study Assessments

Demographics, medical history, New York Heart Association (NYHA) functional class and HRQoL – Minnesota Living with Heart Failure Questionnaire (MLHFQ) and Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) [3, 17] – were assessed. The 6-min walk distance (6MWD) test was performed according to guidelines [18]. Heart rate, systolic and diastolic blood pressure as well as arterial oxygen saturation (SaO_2) were assessed before and at the end of the 6MWD test.

A Mini Mental State Examination (MMSE) and a clock test were conducted at baseline, and the patients' educational level was assessed. Patients underwent cognitive testing at baseline and at FU after 3 months, including the Trail Making Tests (TMTs) A and B that are validated tools for measuring processing speed (part A) and executive function (part B) [19, 20]. The Stroop tests are considered measures of cognitive flexibility and control as well as of executive functioning [21]. The Five-Point Test (5PT) [22] is used to examine figural fluency. All three are widely accepted instruments for cognitive testing. On TMT A and B, we used normative data of a Swiss sample, stratified by age and gender and corrected for education level [19, 20]. For the Stroop test and the 5PT, we used age- and education-stratified normative data that were collected in North America and Germany, respectively [21, 22]. An abnormal result in the cognitive tests was defined as a score deviating by more than 2 standard deviations (SD) from the mean normative data.

All patients had standard RHC, including assessments of the heart rate, mean arterial and pulmonary artery pressure, pulmonary artery wedge pressure and right atrial pressure. The cardiac output was continuously measured by thermodilution (Vigilance II, Edwards Lifesciences, Irvine, Calif., USA). Systemic and pulmonary vascular resistance and the cardiac index (cardiac output divided by body surface area) were calculated.

Blood Analysis and Oximetry

During catheterization, arterial and mixed venous blood gases were immediately analyzed (oxygen saturation at rest, arterial pH, arterial partial pressure of oxygen and carbon dioxide), and the arterial blood gas analysis was repeated after 3 months of FU (ABL 90 FLEX blood gas analyzer, Radiometer GmbH). NT-pro-BNP and highly sensitive C-reactive protein were determined in venous blood samples in the central hospital laboratory by ELISA at baseline and after 3 months.

Cerebral and Muscle Tissue Oxygenation by Near-Infrared Spectroscopy

CTO and quadriceps muscle tissue oxygenation (QMTO) were recorded by near-infrared spectroscopy (NIRS; INVOS, Somanetics Corporation, Troy, Mich., USA) in a supine position after at least 10 min of rest and averaged over the following 10 min of rest at the day of RHC and after 3 months of FU. Two optic sensors (optodes) were placed on the left and right forehead above the frontal sinus and bilaterally above the vastus medialis of the quadriceps muscles. CTO and QMTO were measured in 6-second intervals. NIRS data from the left and right body sites were analyzed, and the signal with the averaged highest value was taken for final analysis.

Statistics

SPSS 22 (SPSS Inc., Chicago, Ill., USA) and Excel (Microsoft Office package) were used for statistical analyses. Data were summarized by medians (quartiles) due to the small sample size and mostly non-normal distributions. Changes from baseline to FU were evaluated using Wilcoxon's matched-pair test. Pearson's correlation and stepwise multiple regression were used for uni- and multivariate

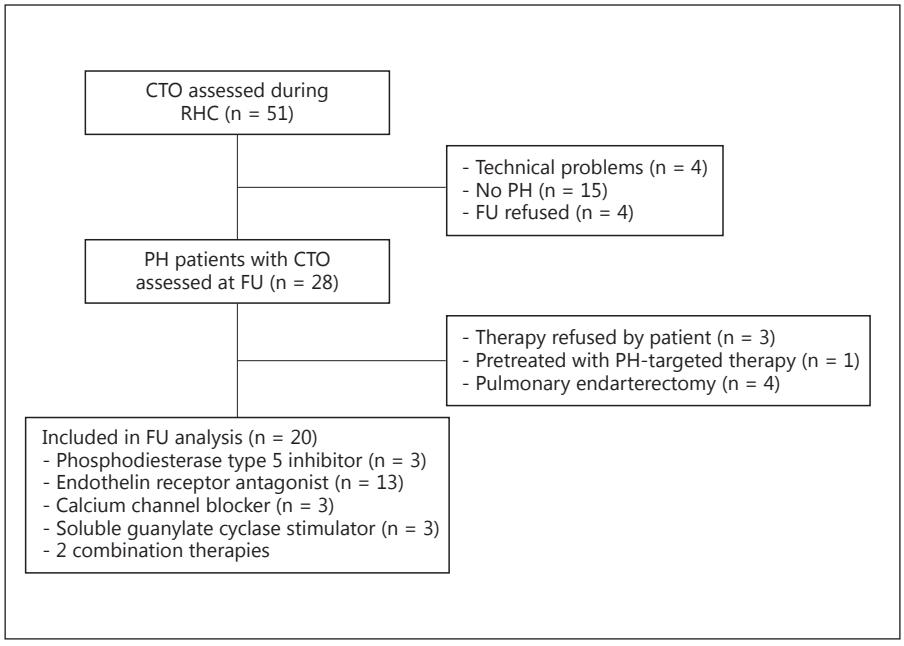

Fig. 1. Flow diagram of patients scheduled for RHC included in the study and analyzed.

Table 1. Baseline characteristics

Participants (females)	20 (13)
Age, years	66 (44; 73)
Body mass index	25 (23; 28)
NYHA Class (II, III, IV)	8 (40), 10 (50), 2 (10)
Education level, years	12.5 (10.5; 15)
MMSE, points	29 (29; 30)
Classification	
PAH	15 (75)
Idiopathic	9 (45)
Associated with connective tissue disease	5 (25)
Associated with portal hypertension	1 (5)
Inoperable chronic thromboembolic PH	5 (25)
Treatment started	
Endothelin receptor antagonist	13
Phosphodiesterase 5 inhibitor	4
Soluble guanylate cyclase stimulator	3
Calcium channel blocker	1
Combination therapy[1]	1
Hemodynamics	
Heart rate, beats/min	77 (68; 86)
Systolic blood pressure, mm Hg	125 (116; 149)
Diastolic blood pressure, mm Hg	80 (74; 89)
Mean pulmonary arterial pressure, mm Hg	37 (30; 49)
Cardiac index, l/min/m^2	3.3 (2.6; 3.7)
Pulmonary vascular resistance, dynes × s × m^2	395 (211; 477)

Values are given as numbers (percentages) or medians (quartiles). Cardiac index = Cardiac output/body surface area.

[1] Combination therapy: endothelin receptor antagonist/phosphodiesterase 5 inhibitor.

Table 2. Changes after 3 months

Cognitive tests	Baseline	FU after 3 months	Δ (SD)
5PT, total, n	33 (26; 39)	36 (29; 46)	2 (8)
5PT, invalid, n	3 (1; 9)	4 (1; 8)	−1.5 (7.5)
5PT, invalid, %	9.7 (1.4; 30.2)	11 (1; 25)	−2.9 (13.1)
TMT A, time, s	37 (27; 55)	30 (24; 42)	−3.8 (21)*
TMT B, time, s	92 (56; 135)	76 (57; 136)	−4.3 (47.7)
Stroop test 1, time, s	17 (13; 21)	15 (12; 18)	−1.6 (6)
Stroop test 2, time, s	18 (16; 22)	16 (15; 20)	−2.8 (3.7)**
Stroop test 3, time, s	29 (24; 37)	28 (22; 39)	0.6 (9.7)
Functional, vital and blood parameters			
NYHA functional class	3 (2; 3)	2 (2; 3)	−0.4 (0.7)*
6MWD, m	508 (364; 602)	543 (365; 625)	18 (44)*
Heart rate, bpm	83 (71; 91)	86 (76; 94)	4 (17)
Systolic blood pressure, mm Hg	125 (116; 149)	118 (111; 130)	−10.5 (16.4)*
Diastolic blood pressure, mm Hg	80 (74; 89)	76 (70; 87)	−3.3 (10.3)
SpO_2 peak walk, %	91 (88; 94)	93 (85; 97)	0.1 (5)
Heart rate peak walk, bpm	109 (101; 131)	110 (99; 129)	−1 (15)
NT-proBNP, ng/l	278 (110; 1,920)	159 (77; 1,842)	−339 (1,606)
C-reactive protein, mg/l	2.4 (1.3; 9.0)	2.5 (1.3; 6.6)	−2.4 (8.8)
Blood and tissue oxygenation			
Arterial partial pressure of oxygen, kPa	9.6 (8.1; 10.6)	10.3 (8.8; 11.3)	0.8 (0.8)**
Arterial partial pressure of carbon dioxide, kPa	4.7 (4.4; 5.1)	4.7 (4.3; 5.0)	−0.02 (0.46)
SaO_2, measured in hemoglobin, %	94 (90, 95)	95 (93; 96)	1.5 (2.2)*
Cerebral tissue oxygenation, %	66 (61; 70)	65 (58; 69)	0.2 (7.7)
QMTO, %	82 (75; 83)	83 (76, 90)	3.9 (8.2)
QoL			
CAMPHOR symptoms, points	8 (4; 14)	5 (3; 11)	−2.5 (4.5)*
CAMPHOR activity, points	4 (2; 11)	4 (2; 8)	−1 (4.5)
CAMPHOR QoL, points	4 (1; 8.5)	3 (1; 11)	−0.5 (4.5)
MLHFQ general, points	32 (12; 54)	19 (11; 33)	−10 (21)
MLHFQ physical, points	18 (9; 23)	11 (5; 14)	−5.5 (9.5)*
MLHFQ emotional, points	7 (2; 13)	5 (2; 10)	−2 (6.5)

Values are given as medians (quartiles) and differences in means (SD). * $p < 0.05$; ** $p < 0.01$.

analysis. We used 3 different cognitive tests providing a total of 11 parameters and 2 different HRQoL tests providing 6 parameters. As the respective cognitive and HRQoL parameters intercorrelated, the parameters were converted into one new component each for cognition and HRQoL at baseline and FU using dimension reduction. A p value <0.05 was taken for statistical significance.

Results

Patients

From the 51 subjects who underwent RHC with NIRS assessment, 20 patients were newly diagnosed with PH and had medical therapy (fig. 1). Characteristics are shown in table 1. PH-targeted treatment during the 3 months of FU consisted of endothelin receptor antagonists (n = 13), phosphodiesterase 5 inhibitors (n = 4), soluble guanylate cyclase stimulators (n = 3) or calcium channel blockers (n = 1). One patient received combination therapy.

Baseline Cognitive Testing

At baseline, 2 (4%) patients had a pathologic TMT, 5 (25%) had an abnormal Stroop test (1, 2 or 3) and 9 (45%) had an abnormal 5PT (fig. 2).

Change with Disease-Targeted Therapy

After 3 months of FU, in patients with newly introduced disease-targeted medical treatment, 3 patients

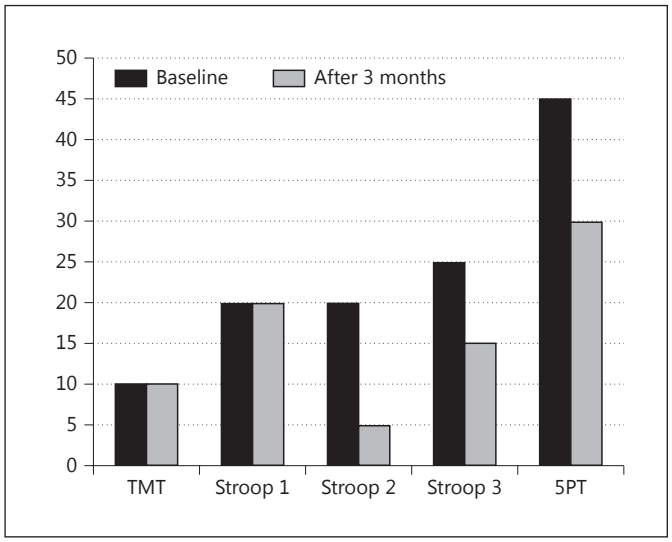

Fig. 2. Percentages of PH patients with abnormal cognitive test results compared to standard populations are shown at baseline and after 3 month of disease-targeted therapies.

normalized their Stroop 2 test, 2 their Stroop 3 test and 3 their 5PT with unchanged other cognitive testing (fig. 2). The scores of the TMT A and Stroop 2 test improved (table 2). There was no change in CTO or QMTO after 3 months of disease-targeted therapy despite the improved blood oxygenation (table 2). NYHA class, 6MWD, arterial and peripheral oxygen saturation, and partial pressure of oxygen improved (table 2). HRQoL domains showed improved scales in the CAMPHOR symptom score and in the MLHFQ physical scale. Amongst parameters with significant changes, the calculated effect size (mean change divided by SD of the baseline) was 0.36 for the CAMPHOR symptom scale, 0.35 and 0.16 for the TMT A and Stroop 2 test time, and 0.13 for the 6MWD test.

Predictors of Cognitive Function, Exercise Capacity and HRQoL

Regression analysis with cognitive function at baseline and at FU as dependent factors showed that baseline CTO and the 6MWD test remained independent predictors in multivariate models (table 3). The level of education, measured in years, correlated only with the baseline TMT B score (R = –0.512, p = 0.021) and the number of errors in the Stroop 3 test (R = –0.499, p = 0.025).

The 6MWD correlated with age, NYHA class, HRQoL, cognitive function, CTO, QMTO, SaO_2, $SmvO_2$ and the pulmonary vascular resistance (table 4). Multivariate analysis revealed that baseline CTO was the only independent predictor of 6MWD at baseline as well as at FU.

The baseline HRQoL component correlated with the NYHA class, 6MWD, cognitive function component, the MMSE, CTO as well as SaO_2 and $SmvO_2$ mixed venous oxygen saturation (table 5). The NYHA class and CTO at FU were both independent predictors of HRQoL.

Table 3. Predictors of cognitive function

	Univariate analysis		Multiple regression analysis	
	correlation coefficient (Pearson)	p value	correlation coefficient (R^2)	p value
Age	0.457	0.043		
NYHA class	0.490	0.028		
HRQoL	0.517	0.02		
6MWD	–0.796	0.000	–0.476/*–0.795*	0.019/*0.000*
CTO	–0.805	0.000	–0.805	0.000
SaO_2	–0.681	0.001		

Italicized figures represent the values for the cognitive function during FU as dependent variable.

Table 4. Predictors of the 6MWD

	Univariate analysis		Multiple regression analysis	
	correlation coefficient (Pearson)	p value	correlation coefficient (R^2)	p value
Age	–0.521	0.018		
NYHA class	–0.663	0.001		
HRQoL	–0.511	0.021		
Cognitive function	–0.796	0.000		
CTO	0.752	0.000	0.718/*0.727*	0.000/*0.000*
QMTO	0.356	0.124		
SaO_2	0.605	0.005		
$SmvO_2$	0.740	0.000		
PVR	–0.510	0.022		

Italicized figures represent the values for the 6MWD during FU as dependent variable. PVR = Pulmonary vascular resistance.

Discussion

Our data confirm that up to 45% of PH patients have cognitive deficits compared to reference populations, and we could show for the first time that aspects of cognitive function are improved after 3 months of disease-targeted

Table 5. Predictors of HRQoL

	Univariate analysis		Multiple regression analysis	
	correlation coefficient (Pearson)	p value	correlation coefficient (R^2)	p value
NYHA class	0.697	0.001	0.486/*0.595*	0.001/*0.006*
6MWD	–0.511	0.021		
Cognitive function	0.517	0.02		
MMSE	–0.587	0.006		
CTO	–0.519	0.019	*–0.476*	*0.01*
$SmvO_2$	–0.530	0.016		
SaO_2	–0.208	0.379		

Italicized figures represent the values for the HRQoL during FU as dependent variable.

treatment. Cognitive function correlated with age, CTO and markers of disease severity, and CTO at baseline was the strongest predictor of cognitive function.

Only one study has assessed cognitive function in PH so far and showed impaired cognitive function compared to controls in 57% of patients [2]. The cognitive tests applied included the TMT and the Stroop tests, 2 out of 3 tests used in our study. However, the authors did not evaluate correlations of PH disease markers with cognitive function, and there was no FU.

In the present study, we used the TMT A and B, Stroop tests 1–3 and 5PT, widely accepted instruments for the evaluation of cognitive capacity [19–22]. As the interpretation of cognitive tests should be critically cautious, since they are influenced by education, age and other demographic factors, we compared our results with normative data stratified for age and educational level and thus minimized these confounding factors. We could show that up to 45% of PH patients had abnormal cognitive test results at baseline. Disease-targeted medical therapy was associated with the normalization of 3 of the 5 tests in 15, 10 and 15% (fig. 2). Furthermore, 2 of 5 cognitive scores (Stroop 2 time and TMT A time, evaluating processing speed and executive functioning) improved. The effect size of certain measures of cognitive function even exceeded those of the 6MWD test. Interestingly, we had the chance to follow up a small control group (n = 4) consisting of 3 PH patients who were assessed at baseline and without therapy and 1 patient who already had been prescribed PH-targeted therapy at another hospital without change. These patients did not show improvements in cognitive testing or any other parameter after 3 months (data not shown), supporting our hypothesis that disease-targeted therapy may improve cognitive function in PH. However, a larger control group and randomized controlled trials would be necessary to corroborate this point.

In a previous study, we found that patients with PH had lower CTO during exercise compared to controls and that acute vasodilation with nitric oxide increased CTO in PH patients but not in controls [13]. Thus, we hypothesized that long-term vasodilator therapy might similarly increase CTO in PH patients and, consequently, cognitive function. However, we found that CTO did not improve at FU despite an improved arterial oxygenation. The lack of a change in regional CTO despite an improvement in clinical outcomes (6MWD, cognitive performance) after 3 months of PH-targeted therapy might relate to an increase in cerebral oxygen consumption promoted by an increased cerebral oxygen delivery associated with hemodynamic improvement. Moreover, improved hemodynamics might have enhanced CTO in brain regions other than those monitored with NIRS [23–25]. It has been postulated that the frontal lobe is an equivalent to executive function, which was tested by several of our cognitive tests [26]. However, it is likely that many other brain regions are involved [27, 28]. Processing speed, as assessed by the TMT, seems to be associated with the frontal and the parietal lobe [29]. Additionally, patients after amygdalohippocampectomy have been found to have a decline in figural fluency, as measured in our study by the 5PT [30]. Thus, it may well be that the prefrontal cortex measurements we performed do not sufficiently reflect the CTO of brain regions relevant for cognitive performance. Another potential explanation for an unchanged CTO despite the improvements in arterial oxygenation might be an impaired cerebral autoregulation. The increase in CTO in response to cognitive brain activation declines with physiological aging [31]. This age-dependent decline may either be due to an altered functional brain organization or to an alteration of coupling between brain cell activity and blood flow. In patients aged >65 years, cerebrovascular autoregulation was found to be less efficient compared to younger adults, resulting in a decreased oxygen extraction during compromised cerebral blood flow [31, 32]. The mean age of our participants was 66 years and thus, the missing improvement in CTO may have been caused by age-related defective autoregulation.

We found that baseline CTO was the most powerful predictor of cognitive function and also predicted exercise performance and HRQoL. Thus, despite an unchanged CTO under therapy, CTO is independently correlated with cognitive function and markers of disease

severity. CTO as tissue oxygenation measurement might be closely correlated with the $SmvO_2$, a well-known marker of disease severity. However, in our collective, CTO was clearly the best predictor of exercise capacity, HRQoL and cognitive function and performed much better than invasively or noninvasively measured arterial or mixed venous blood oxygenation or muscle tissue saturation. Thus, noninvasively measuring CTO using NIRS at baseline may be a time- and cost-efficient technique to predict cognitive and exercise performance in PH.

Several authors could show associations between cognitive decline and HRQoL in pulmonary disease [33, 34]. White et al. [2] hypothesized that HRQoL and cognitive function were associated in PH patients; however, they failed to confirm this. One of their explanations was that they did not use a PH-specific questionnaire for HRQoL. In our study, we used PH-specific and well-evaluated questionnaires and could show that the component for cognitive function and HRQoL had a positive correlation (table 3). However, multivariate analysis revealed that only functional class assessment and CTO were independent predictors of HRQoL. This might be partly explained by an intercorrelation between HRQoL symptom scales and NYHA functional class ($R^2 = 0.697$ for baseline and 0.600 for FU). This is in line with other studies that found an association of low NYHA class with better HRQoL and high NYHA class with worse HRQoL in PH patients [35, 36]. In line with others, we could confirm a correlation between HRQoL and exercise performance [4–6].

As in many previous studies, we confirmed that the 6MWD test improves with PH-targeted treatment [37–39]. We found a good correlation between CTO and the 6MWD test, but not with QMTO [13]. We previously showed that CTO at maximal exercise was predictive of the maximal workload achieved, but QMTO was not. This points towards a role of the CTO decline and thus the brain in exercise limitation in PH patients. Our work reinforces several studies that postulate that CTO is a limiting factor for maximal exercise performance in a healthy population and in cardiorespiratory disease patients [12–15].

The main limitations of this study are the small patient collective and a relatively short time of observation. However, PH is a rare disease and thus, the number of incident patients consenting to clinical trials is limited. As we focused on incident PH patients who were treated after diagnosis, we have no formal control group for this study. We did not include a prevalent control group on stable therapy. Although we used different cognitive tests in order to have a comprehensive insight into cognitive function, every single cognitive test has its limitation and reflects only a specific part of the complex human cognitive system. Furthermore, repeated measurements may be influenced by learning effects. To reduce practice effects, we let the patients practice all tests before testing. The unchanged cognitive performance in 4 patients who had no PH-targeted therapies might indicate that cognitive function improves in response to PAH-targeted therapy.

In summary, PH is associated with cognitive impairment, and disease-targeted therapy may improve cognitive function. CTO was the strongest predictor of cognitive performance, but also exercise capacity and HRQoL.

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Financial Disclosure and Conflicts of Interest

No conflicts of interest regarding this study are declared by the authors.

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